Original research

Cardiovascular risk and obesity impact loss of grey matter volume earlier in males than females

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ABSTRACT

Background It remains imperative to discover the time course that cardiovascular risk factors influence neurodegeneration in males and females and decipher whether the apolipoprotein (APOE) genotype mediates this relationship. Here we perform a large-scale evaluation of the influence of cardiovascular risk and obesity on brain volume in males and females in different age groups.

Methods 34 425 participants between the ages of 45 and 82 years were recruited from the UK Biobank database https://www.ukbiobank.ac.uk. T1-weighted structural MR images (n=34 425) were downloaded locally for all participants, and voxel-based morphometry was performed to characterise the volumetric changes of the whole brain. The influence of Framingham cardiovascular risk (general cardiovascular risk), abdominal subcutaneous adipose tissue, and visceral adipose tissue volume (obesity) on cortical grey matter volume across different decades of life was evaluated with voxel-wise analysis.

Results In males, cardiovascular risk and obesity demonstrated the greatest influence on lower grey matter volume between 55–64 years of age. Female participants showed the greatest effect on lower grey matter volume between 65–74 years of age. Associations remained significant in APOE ε4 carriers and APOE ε4 non-carriers when evaluated separately.

Conclusions The strongest influence of cardiovascular risk and obesity on reduced brain volume was between 55–64 years of age in males, whereas women were most susceptible to the detrimental effects of cardiovascular risk a decade later between 65–74 years of age. Here we elucidate the timing that targeting cardiovascular risk factors and obesity should be implemented in males and females to prevent neurodegeneration and Alzheimer's disease development.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cardiovascular risk factors including obesity are associated with an elevated risk of dementia development.

WHAT THIS STUDY ADDS

⇒ Males are most susceptible to the detrimental influence of cardiovascular risk a decade earlier than females, with temporal lobe regions particularly vulnerable to the damaging effects.

⇒ Cardiovascular risk and obesity show a bell-shaped relationship with neurodegeneration over time in APOE ε4 carriers and APOE ε4 non-carriers.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results suggest that mitigating cardiovascular risk is an important therapeutic target in the prevention of Alzheimer's disease, and indicate that this should be addressed aggressively a decade earlier in males than in females independent of their APOE ε4 status.

INTRODUCTION

Alzheimer's disease currently affects ~50 million people worldwide[1] and, despite an increasing economic and social burden, few treatment options exist. Alzheimer's disease pathogenesis is multifactorial involving the accumulation of toxic proteins (amyloid and τ), neuroinflammation, synaptic dysfunction, oxidative stress, and insulin resistance.[2 3] While anti-amyloid therapies have shown promise, it remains imperative to identify effective disease-modifying therapeutic strategies for Alzheimer's disease. This will likely require several compounds that target individual pathologies.[4] Strategies that influence cardiovascular risk could

have potential benefits in preventing neurodegenerative processes as a potential novel therapeutic strategy. However, it is important to identify the therapeutic window when cardiovascular risk intervention will prevent neurodegenerative processes.

Cardiovascular risk factors including type 2 diabetes, obesity, hypertension, and smoking are associated with an augmented risk of dementia development.[5] The 2017 and 2020 Lancet commissions established 12 modifiable risk factors for dementia including hypertension, smoking, obesity, and diabetes.[6] Obesity may be related to Alzheimer's disease pathology via dysregulated endocrine homeostasis.[7] The production of pro-inflammatory adipokines include leptin, adiponectin, C-reactive protein, and pro-inflammatory cytokines by adipocytes. Adipose tissue can be infiltrated by immune cells, which in visceral obesity may switch to pro-inflammatory macrophages.[7] Pro-inflammatory mediators could cross the blood-brain barrier (BBB) and trigger neurodegenerative pathways. Increasing evidence supports the role of leptin in the regulation of the synaptic function of hippocampal neurons.[8] Reduced leptin signalling within the brain could impair hippocampal function and result in cognitive deficits.[8] Moreover, ghrelin levels are diminished in obesity which has important implications considering its protective role for the central

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nervous system; ghrelin promotes neuroplasticity and cognitive function and regulates microglial activity.[9]

Identifying the precise timing of when cardiovascular risk significantly influences neurodegenerative processes is essential to establish the therapeutic window that mitigating cardiovascular risk could exert maximal therapeutic benefit. There is little research establishing sex differences in the relationship between cardiovascular risk and brain health over the life span. Sex hormones including oestrogen and testosterone exert neuroprotective effects, including protecting neuronal loss and preventing oxidative damage.[10] The mean age of menopause is 46 years in women which results in the relatively rapid loss of ovarian hormones, whereas there is a gradual loss in androgen levels over time in men.[11] It is important to decipher whether sex differences mediate the role of cardiovascular risk on brain atrophy, which may be critical for therapies aimed at treating neurodegenerative diseases.[10] Furthermore, it remains imperative to establish the influence of apolipoprotein (APOE) genotype on the relationship between cardiovascular risk and neurodegeneration.

The aim of this study was to: (1) evaluate the influence of cardiovascular risk on neurodegeneration in males and females and during different age groups; (2) assess whether cardiovascular risk mediates neurodegenerative processes in APOE ε4 carriers and APOE ε4 non-carriers; and (3) evaluate the influence of abdominal fat and visceral obesity on neurodegeneration.

METHODS
Study population
A total of 34 425 participants had structural T1-weighted MRI brain scans which could be used for analysis after quality control check and abdominal MRI scans and were enrolled into the study from the UK Biobank database. The UK Biobank is a prospective study which aimed to recruit ~500 000 participants between 2006 and 2010.[12] Since 2014, a subset of 100 000 participants were invited to undergo brain and abdominal MRI. Details of recruitment and methods are available at https://www.ukbiobank.ac.uk. Participants had a mean age of 63.6 years (range 45–82 years, SD 7.54). This analysis of data was performed under UK Biobank application ID87031.

Measures
Cardiovascular risk
Framingham general cardiovascular risk
The Framingham score provides a sex-specific risk prediction algorithm.[13] The score is based on core cardiovascular risk factors: age, high-density lipoprotein, total cholesterol, systolic blood pressure, treatment for blood pressure, smoking status, and diabetes. See D'Agostino *et al* for the cardiovascular risk calculation.[13] Risk scores were not calculated for participants with missing data (n=10 671).

Abdominal MRI
Abdominal MRI imaging was performed using Siemens 1.5T MAGNETOM Aera using a 6 min dual-echo Dixon Vibe protocol, covering the neck to the knees. Six overlapping slabs were acquired covering a total of 1.1 m. Slab acquisition parameters were: TR (repetition time) 6.69 ms, TE (time to echo) 2.39/4.77 ms, and bandwidth 440 Hz. Abdominal subcutaneous adipose tissue and visceral adipose tissue volumes were collected for all participants as a marker of obesity. MRI is the gold standard method of measuring body fat composition, outperforming anthropometric measures (eg, body mass index (BMI)) as predictors of body fat distribution and associated cardiovascular risk.[14]

Abdominal subcutaneous adipose tissue volumes reflect the amount of adipose tissue beneath the skin, while visceral adipose tissue is adipose tissue which lines internal organs. Both abdominal subcutaneous adipose tissue and visceral adipose tissue are associated with adverse cardiovascular outcomes, including insulin resistance, metabolic syndrome, and hypertension.[15]

Details of image analysis of abdominal MRI performed consisted of (1) image calibration, (2) fusion of image stacks, (3) image segmentation, and (4) quantification of fat and muscle volumes including manual quality control. The details of this analysis are reported elsewhere.[14 16]

Apolipoprotein E gene
Genotyping was performed using the UK Biobank Axiom Array to evaluate APOE genotype for all participants where biospecimen data were available. Single nucleotide polymorphisms for the rs429358 and rs7412 alleles were acquired. A total of 5715 participants had missing genotype data and APOE genotyping was not performed.

Structural T1-weighted MRI
Structural brain imaging was performed on a standard Siemens Skyra 3T, with a standard Siemens 32-channel radiofrequency (RF) receive head coil[17]; resolution 1×1×1 mm, field of view (FOV) 208×256×256. All structural scans (n=34 425) were downloaded locally at Imperial College London for image processing and statistical analysis.

Optimised voxel-based morphometry
Voxel-based morphometry (VBM) is a neuroimaging technique that enables the detection of changes in brain volume through voxelwise statistical evaluation of multiple brain images. This technique can evaluate grey matter volume changes across cortical regions without a priori assumptions where regional effects may occur. VBM analysis was utilised to overcome issues associated with regional analysis (region-of-interest analysis) which can be confounded by researcher bias, the timeline from study conception to analysis and interpretation that the selection of the region of interest is made, and limiting the analysis to a subset of regions.[18] VBM enabled the evaluation of the influence of cardiovascular risk, abdominal subcutaneous adipose tissue, and visceral adipose tissue on neurodegeneration across the cortex. VBM was conducted using Statistical Parametric Mapping (SPM12; www.fil.ion.ucl.ac.uk/spm) software on all structural T1-weighted MRI scans to perform voxel-level analysis between cardiovascular risk and brain atrophy. Scans were segmented into different tissue probability classes, with grey and white matter images saved in native space and a format suitable for DARTEL import; otherwise, default SPM12 segmentation settings were used. A study-specific template was created in DARTEL using a subset of 1000 participants to reduce the computational requirements. The Python module, Scikit-learn, was used to select participants for DARTEL randomly. To generate a representative sample, the randomised selection of participants was stratified by biological sex and age group. Non-linear registration to the study-specific template was then performed to produce Jacobian determinants for all participants. Then grey and white matter images were transformed to the study-specific template in MNI (Montreal Neurological Institute) space, smoothed with a Gaussian kernel full-width at half-maximum (FWHM) (8×8×8 mm) and with Jacobian modulation applied to preserve local tissue volumes. A total cerebral grey matter mask was applied (volume=198 452 voxels). This enabled the exploration

Table 1 Descriptive statistics

Age group (years)	Male				Female			
	45–54	55–64	65–74	75+	45–54	55–64	65–74	75+
n	2175	5395	7001	1314	2899	7382	7259	999
Mean age (years)	51.6±1.93	59.9±2.85	69.2±2.70	76.5±1.53	51.6±1.95	59.8±2.85	68.9±2.70	76.5±1.49
APOE status non-carriers/homozygotes/heterozygotes (%)	71.2/26.7/2.1	72.2/25.8/2.0	73.7/24.2/2.1	73.5/24.2/2.3	70.2/27.2/2.6	71.5/26.1/2.4	72.8/25.1/2.1	73.9/24.8/1.2
Mean abdominal subcutaneous adipose tissue (ASAT) volume	6.08±2.81	5.93±2.55	5.73±2.32	5.37±1.94	7.99±3.76	8.11±3.57	7.68±3.12	7.27±2.72
Mean visceral adipose tissue (VAT) volume	4.56±2.28	4.86±2.29	4.99±2.28	4.91±2.22	2.31±1.46	2.66±1.59	2.78±1.53	2.86±1.46
Mean total cardiovascular risk points	11.0±2.74	14.1±2.63	16.7±2.62	18.8±2.31	7.79±3.40	11.2±3.52	14.7±3.29	17.2±3.04
Mean cardiovascular risk (%)	12.2±5.68	19.3±6.59	25.5±5.54	28.9±2.86	5.10±3.31	8.73±5.04	14.3±6.59	19.8±6.90

of the volume and percentage of grey matter voxels inside the mask that reached the statistical threshold, indicating the effect on neurodegenerative processes induced by cardiovascular risk.

Total intracranial volume

Corrections for individual variations in head size is a recommended practice for VBM studies,[19 20] and is implemented in this study. Processed data for the estimated total intracranial volume was obtained from the UK Biobank for all participants. Structural T1-weighted images were processed via Freesurfer version 6.0 (https://surfer.nmr.mgh.harvard.edu/),[21] using the standard 'recon-all' pipeline. Briefly, 'recon-all' performs intensity non-uniformity correction and normalisation, skull stripping, and registration to the fsaverage template. Estimated total intracranial volumes are calculated based on the Talairach transform (see Buckner *et al* for details[22]).

Statistical analysis

Voxelwise analyses were conducted to evaluate the influence of cardiovascular risk, abdominal subcutaneous adipose tissue, and visceral adipose tissue on grey matter volume. VoxelStats[23] implemented on Matlab v2022a was selected to perform voxelwise linear models to overcome the computational requirements from the substantial sample size.

Voxelwise models were performed at a whole group level and on male and female participants in several age cohorts: ages 45–54,
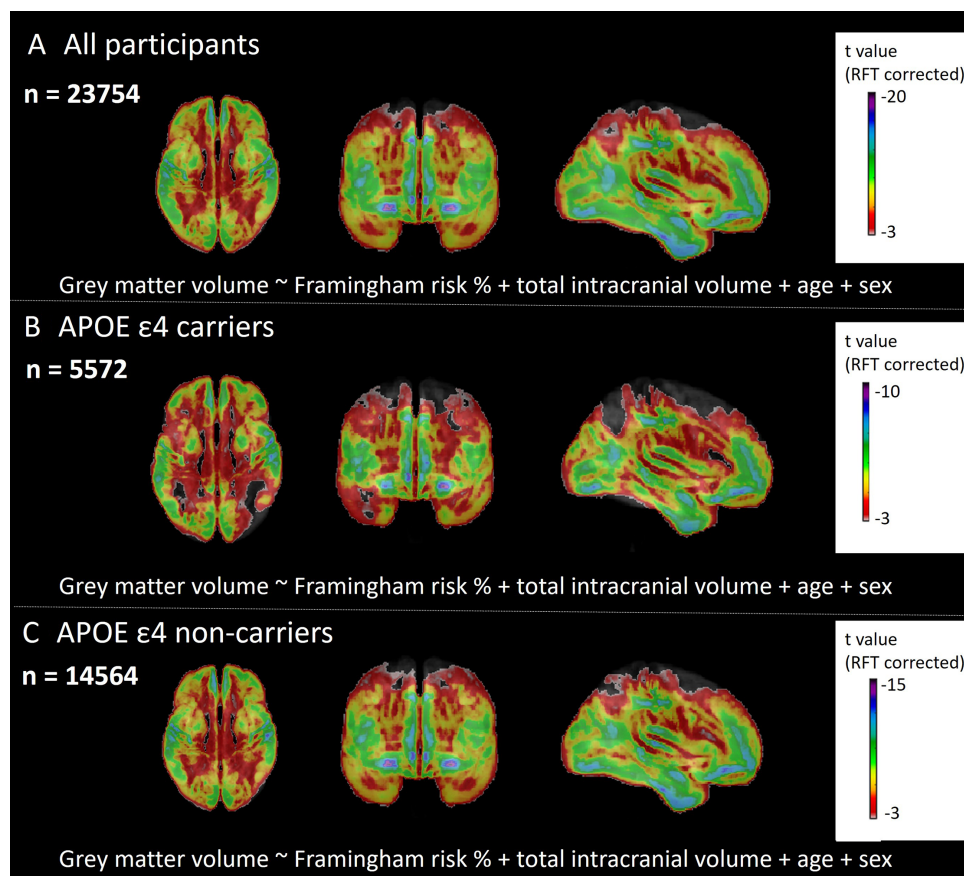
Figure 1 Association between Framingham cardiovascular risk and brain volume. A loss of brain volume was demonstrated in all major lobes, prominent effects were demonstrated in the temporal lobe, thalamus, frontal lobe, and postcentral gyrus. (A) Linear relationship between cardiovascular risk and neurodegeneration in all participants enrolled in the trial. (B) Relationship between cardiovascular risk and neurodegeneration in all APOE ε4 carriers. (C) Relationship between cardiovascular risk and neurodegeneration in all APOE ε4 non-carriers. APOE, apolipoprotein; RFT, random field theory.
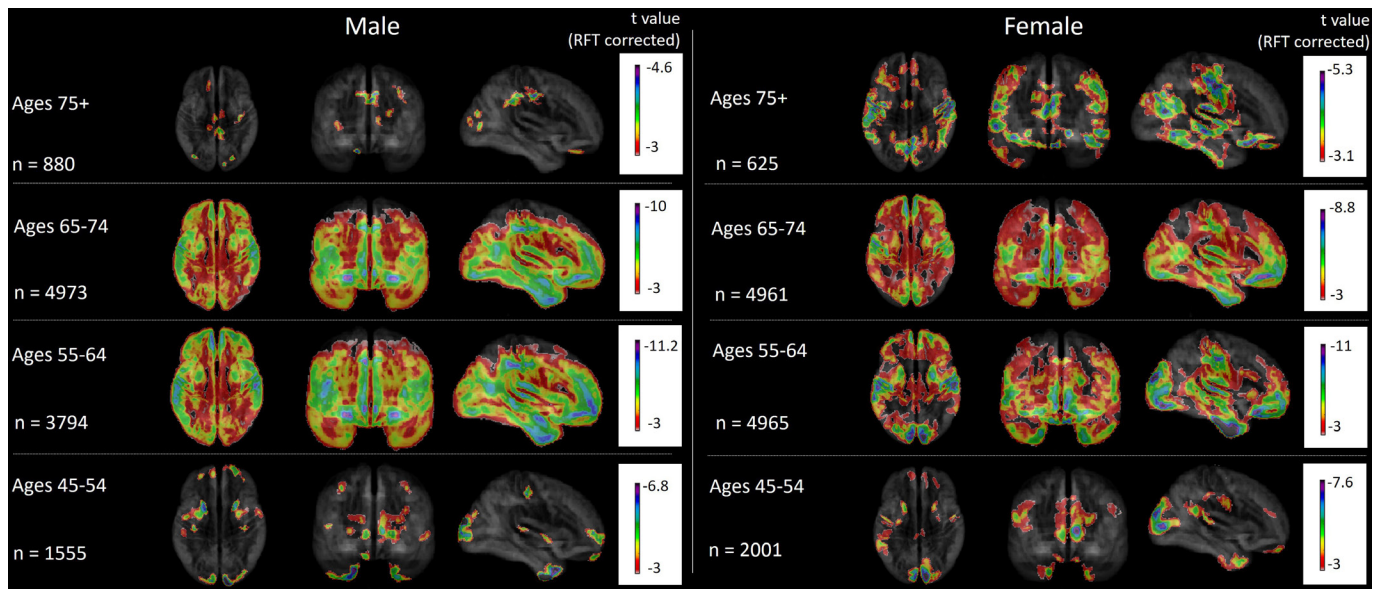
Figure 2 Association between total Framingham risk points and brain volume during different decades in male and female participants. The strongest association between cardiovascular risk and neurodegeneration was shown in male and female participants between the ages of 55–74 years. This relationship was limited to very small brain regions in participants aged 45–54 years and over 75 years of age. These data suggest a bell-shaped relationship between cardiovascular risk and brain atrophy. RFT, random field theory.

55–64, 65–74, and 75+ years; this enabled models to be performed with enhanced statistical power as those with missing APOE genotype (n=5715) were included. To investigate the influence of APOE genotype, voxelwise analysis was also performed in APOE ε4 carriers and APOE ε4 non-carriers. APOE status was dichotomised into two categories based on the presence of the ε4 allele; APOE non-carriers and APOE carriers (ε3/ε4 or ε2/ε4 or ε4/ε4). The role of APOE genotype in the relationship between cardiovascular risk and dementia risk has produced mixed results.[24] As such, to visualise whether cardiovascular risk is associated with lower brain volume independent of the presence of the ε4 allele, separate models were performed for APOE carriers and APOE non-carriers. A random field theory (RFT) based multiple comparisons correction was applied to all linear models[23]; only the voxels that survived the correction were shown. Total intracranial volume was included as a covariate in all models. At a whole group level, sex was selected as a covariate.

Effect of sex
To evaluate the direct effect of sex in the different age cohorts we performed voxelwise models of the interaction of sex and cardiovascular risk (Framingham risk scores, abdominal subcutaneous adipose tissue, and visceral adipose tissue) on brain volume. See the example formula investigating the interaction between Framingham risk scores and sex:

Grey matter volume $\sim b_0 + b_1$Framingham risk score $+ b_2$Sex $+ b_3$(Framingham risk score * Sex) $+ b_4$Total intracranial volume $+ b_5$Age.

RESULTS
Table 1 presents the characteristics of the 34 425 participants enrolled in the study.

Relationship between Framingham cardiovascular risk and brain volume
Framingham risk score was utilised as a marker of cardiovascular risk to investigate the relationship with neurodegeneration, indicated by the association with grey matter volume. At a whole population level (n=23 754), voxelwise results revealed that higher cardiovascular risk was associated with lower grey matter volume across the cortex (figure 1A). Framingham risk score was associated with lower brain volume in 87% of grey matter voxels inside the mask that reached statistical significance ($p<0.001$ RFT corrected). Peak cluster locations were identified in the temporal lobe, thalamus, frontal lobe, and postcentral gyrus. This relationship remained significant in APOE ε4 carriers (figure 1B) and in APOE ε4 non-carriers (figure 1C). This indicates that both APOE ε4 carriers and APOE ε4 non-carriers are at risk of the effects of cardiovascular risk on neurodegeneration.

Male participants
When voxel-wise linear models were performed on male participants during different decades of life, higher cardiovascular risk was associated with lower grey matter volume in all age groups evaluated (figure 2). The strongest relationship was identified in male participants between 55–74 years of age. Cardiovascular risk negatively influenced 67% of grey matter voxels inside the mask, during the decades of 55–64 years and 65–74 years of age. Brain regions indicating the most prominent influence of cardiovascular risk on lower grey matter volume included the temporal lobe.

Interestingly, during the ages of 45–54 years, cardiovascular risk was associated with lower grey matter volume in 2% of grey matter inside the mask. The most prominent effect of cardiovascular risk on neurodegeneration was shown within the temporal lobe, indicating the vulnerability of the temporal lobe in the early stages of the damaging influence of cardiovascular risk. Additionally, in male participants above the age of 75 years, voxel-wise results indicated an association between cardiovascular risk and lower volume in 1% of grey matter inside the mask that reached statistical significance (see table 2).

Female participants
Similarly, in female participants during different decades, higher cardiovascular risk, measured with the Framingham risk score,

Table 2 Cluster information displaying the relationship between Framingham risk score and lower brain volume in male and female participants across different decades

Decade (ages)	Total volume (voxels)	Percentage of grey matter mask volume	Maximum T value	Peak regional associations
Male participants (Framingham risk score)				
75+	1397	1%	−4.54	Posterior cingulate gyrus, precentral gyrus, anterior cingulate gyrus, frontal pole, lateral occipital cortex, juxtapositional lobule cortex
65–74	133 491	67%	−9.94	Temporal pole, precentral gyrus, postcentral gyrus
55–64	133 391	67%	−11.2	Temporal pole, postcentral gyrus, precentral gyrus
45–54	4284	2%	−6.78	Temporal pole, occipital pole, frontal pole, precentral gyrus, planum polare
Female participants (Framingham risk score)				
75+	16 607	8%	−5.28	Supracalcarine cortex, postcentral gyrus, precentral gyrus, frontal orbital cortex, inferior temporal gyrus
65–74	86 097	43%	−8.8	Thalamus, temporal pole, frontal medial cortex, precentral gyrus, postcentral gyrus
55–64	53 641	27%	−11	Temporal pole, occipital pole, frontal medial cortex, postcentral gyrus, posterior cingulate gyrus
45–54	7420	4%	−7.6	Occipital pole, supramarginal gyrus, temporal pole, postcentral gyrus, temporal fusiform cortex

had a negative influence on grey matter volume (figure 2). The strongest detrimental relationship was identified in women aged 65–74 years in a total of 43% of grey matter voxels that reached significance inside the mask. There was a strong negative influence of cardiovascular risk on lower volume in 27% of grey matter inside the mask during the 55–64 years of age.

Participants aged 45–54 years and above 75 years showed a significantly reduced association between cardiovascular risk and lower grey matter volume, suggesting a bell-shaped relationship between the influence of cardiovascular risk on neurodegeneration. Higher cardiovascular risk negatively influenced 4% of grey matter inside the grey matter mask in female participants between 45–54 years of age and 8% of grey matter inside the mask in those over 75 years of age. However, the limited effects in the oldest age group (75+) in males and females may be limited by the relatively small sample size compared with other age groups assessed in this study.

Relationship between obesity and brain volume
To explore the relationship between obesity and grey matter volume, abdominal subcutaneous adipose tissue and visceral adipose tissue volumes were evaluated in 34 425 participants. Abdominal subcutaneous adipose tissue and visceral adipose tissue volumes showed widespread associations with lower grey matter volume (figure 3). Higher abdominal subcutaneous adipose tissue volume negatively influenced 61% of grey matter inside the mask. Similarly, greater visceral adipose tissue volume was associated with lower volume in 64% of grey matter inside the mask that reached statistical significance. Peak cluster coordinates were identified within the temporal pole, thalamus, frontal pole, frontal medial cortex, postcentral gyrus, and precentral gyrus. Associations remained when APOE ε4 carriers and APOE ε4 non-carriers were analysed separately (figure 3).

Male and female participants (abdominal subcutaneous adipose tissue and visceral adipose tissue volumes)
In male and female participants, higher abdominal subcutaneous adipose tissue volume (figure 4) and visceral adipose tissue (figure 4) had the most extensive detrimental influence in male participants aged 55–64 years, and those aged 64–74 years. In males, a significant association between lower grey matter volume and higher subcutaneous identified adipose tissue and visceral adipose tissue volumes was shown in participants aged 45–54 years. However, in male participants over the age of 75 years, higher adipose tissue volumes were only associated with lower grey matter volume in ≤2% of grey matter inside the mask.

The relationship between abdominal subcutaneous adipose tissue volume and visceral adipose tissue with lower grey matter volume was reduced in females aged 45–54 years and those over the age of 75 years (see table 3).

Effect of sex on the relationship between cardiovascular risk and grey matter volume
To identify whether the relationship between cardiovascular risk and grey matter volume differs between male and female participants, we performed linear models with an interaction effect in the different age groups.

Framingham risk scores
No interaction effect was shown at the earliest age group assessed (45–54 years). In those aged 55–64, an interaction effect was demonstrated in 42% of grey matter voxels inside the mask between sex and Framingham risk scores (figure 5), indicating lower grey matter volume in male participants as cardiovascular risk increased. To a lesser extent, this interaction effect was also demonstrated in those aged 65–74 (table 4). This indicates that the detrimental impact of cardiovascular risk is greater and occurs at an earlier stage in males.

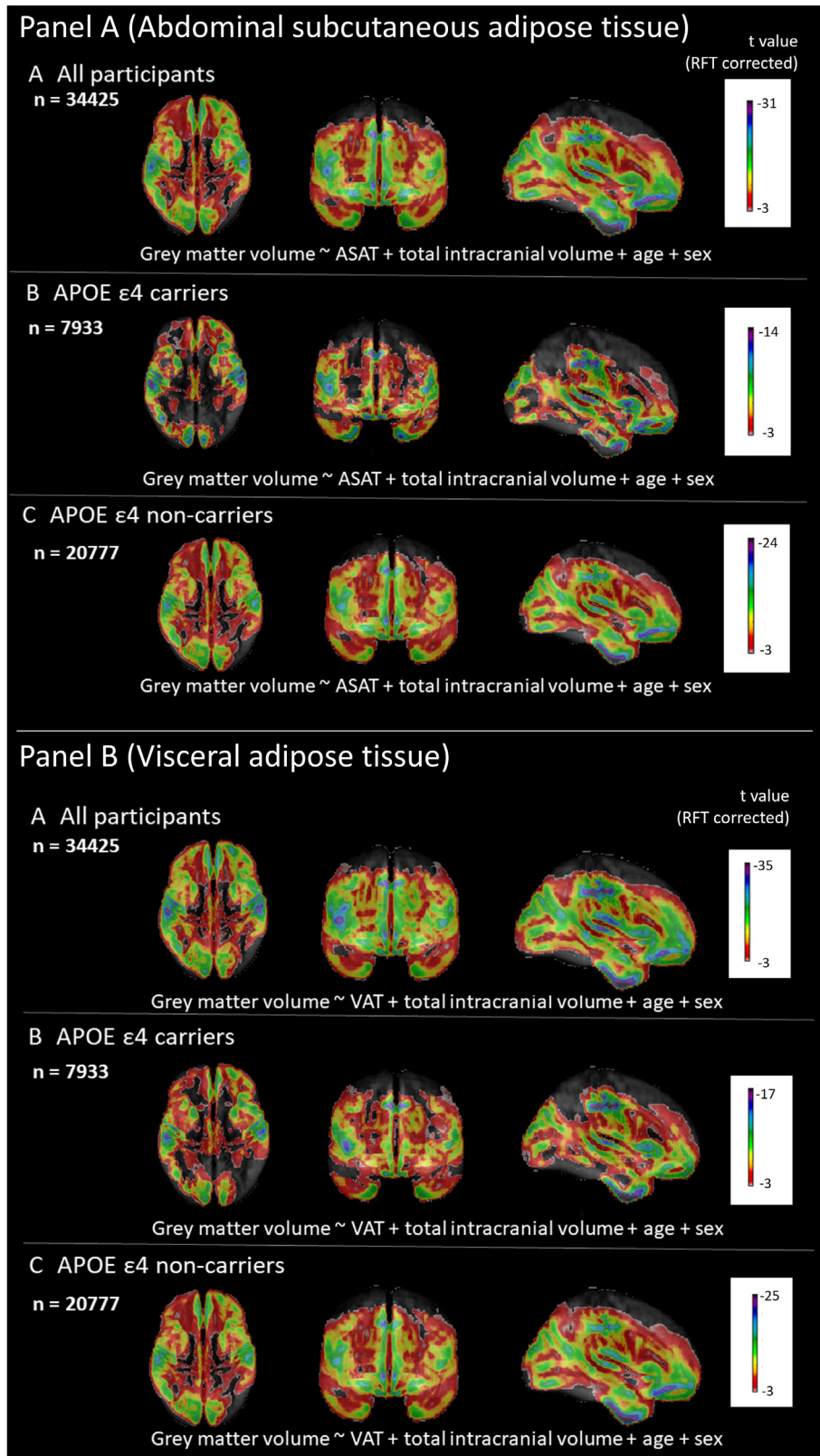#### Abdominal subcutaneous adipose tissue
There was an interaction effect between abdominal subcutaneous adipose tissue and sex on lower grey matter volume in males aged 45–54 (figure 5), 55–64, and 65–74 years.

An interaction between abdominal subcutaneous adipose tissue and sex on lower grey matter volume indicated lower volume in females in those aged 75+ years (table 4).

Visceral adipose tissue
An interaction between visceral adipose tissue and sex on lower grey matter volume was demonstrated in male participants aged 45–54 years (figure 5). This interaction demonstrated that male sex and higher visceral adipose tissue were associated with lower grey matter volume in 8% of voxels inside the mask.

In later life (65–74 years), an interaction was shown between visceral adipose tissue and female sex with lower grey matter volume (table 4).

Figure 3 Association between abdominal subcutaneous adipose tissue volume, visceral adipose tissue volume and brain volume. Panel A: Relationship between abdominal subcutaneous adipose tissue and brain atrophy. (A) Relationship between abdominal subcutaneous adipose tissue volume and neurodegeneration in all participants enrolled on the trial. (B) Relationship between abdominal subcutaneous adipose tissue volume and neurodegeneration in all APOE ε4 carriers. (C) Relationship between abdominal subcutaneous adipose tissue volume and neurodegeneration in all APOE ε4 non-carriers. Panel B: Relationship between visceral adipose tissue and brain atrophy. (A) Relationship between visceral adipose tissue volume and neurodegeneration in all participants enrolled in the trial. (B) Relationship between visceral adipose tissue volume and neurodegeneration in all APOE ε4 carriers. (C) Relationship between visceral adipose tissue volume and neurodegeneration in all APOE ε4 non-carriers. APOE, apolipoprotein; ASAT, abdominal subcutaneous adipose tissue; RFT, random field theory; VAT, visceral adipose tissue.
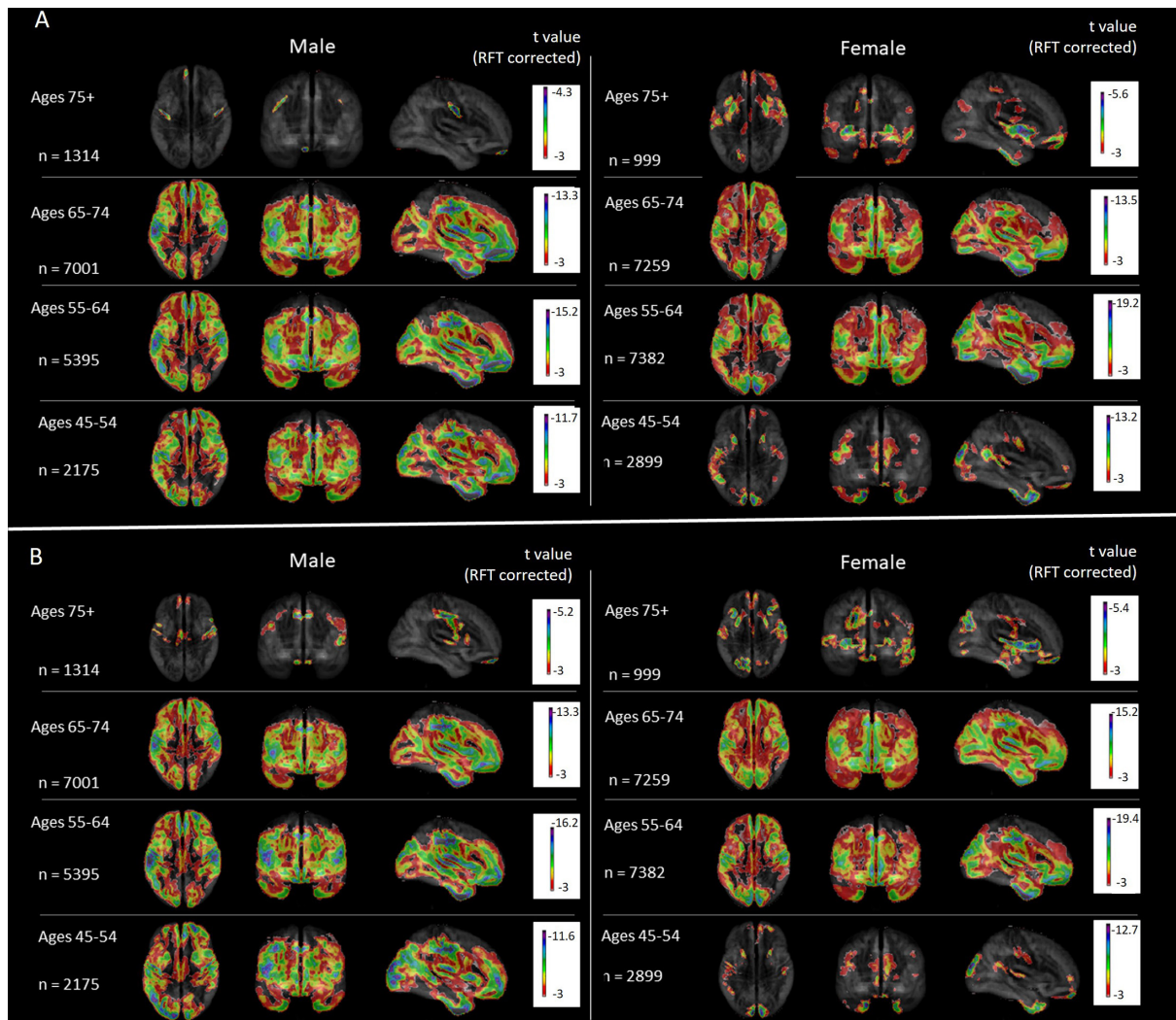
Figure 4 (A) Association between abdominal subcutaneous adipose tissue volume and brain volume during different decades. Abdominal subcutaneous adipose tissue volume shows extensive association with brain atrophy in male and female participants aged 55–74 years and in male participants aged 45–54 years. (B) Association between visceral adipose tissue volume and brain volume during different decades. Abdominal visceral tissue volume shows extensive association with brain atrophy in male and female participants aged 55–74 years and in male participants aged 45–54 years. RFT, random field theory.

DISCUSSION

This study demonstrates that the strongest influence of cardiovascular risk and obesity on neurodegeneration occurs a decade earlier and is sustained over two decades in males compared with females; the influence was also more pronounced in males compared with females. The strongest influence of cardiovascular risk and obesity on neurodegeneration was between 55–74 years in males and 65–74 years in females. We demonstrate that high cardiovascular risk and obesity predispose to gradual loss of brain volume across cortical regions over several decades, occurring in a bell-shaped manner over time. This relationship between cardiovascular risk and neurodegeneration was shown in APOE ε4 carriers and APOE ε4 non-carriers. The detrimental impact of cardiovascular risk was widespread throughout cortical regions, highlighting how cardiovascular risk can impair a range of cognitive functions. Therefore, modifiable cardiovascular risk factors, including obesity, deserve special attention in the treatment/prevention of neurodegenerative diseases, including Alzheimer's disease. This highlights the importance of aggressively targeting cardiovascular risk factors before the age of 55 years to prevent neurodegeneration and Alzheimer's disease, in addition to the benefit of preventing other cardiovascular events such as myocardial infarction and stroke.

Here, we utilised data from the UK Biobank to provide a comprehensive evaluation of the influence of cardiovascular risk on neurodegeneration in over 34 000 participants over several decades. Additionally, we utilised visceral and subcutaneous fat measurements to provide a reliable marker of obesity and APOE genotype to assess whether the presence of the ε4 allele modulates the relationship between cardiovascular risk and neurodegeneration. Voxel-wise linear regression showed that an elevated Framingham cardiovascular risk score and higher abdominal fat were associated with decreased brain volume across the cortex. Prominent effects were identified in temporal lobe structures, regions affected early in Alzheimer's pathogenesis. This highlights the risk of memory impairments and Alzheimer's disease development in those with greater cardiovascular risk. Demonstration of the influence of cardiovascular risk at an early age in males in comparison to females is novel and has not been demonstrated before. In this study, we demonstrate that the influence of cardiovascular risk was widespread and was apparent in all major brain lobes.

Table 3 Cluster information displaying the relationship between abdominal subcutaneous adipose tissue volume, visceral adipose tissue volume and lower brain volume in male and female participants across different decades

Decade (ages)	Total volume (voxels)	Percentage of total grey matter mask	Maximum T value	Peak regional associations
Male participants (abdominal subcutaneous adipose tissue volume)				
75+	443	>1%	−4.29	Precentral gyrus, frontal pole
65–74	80 593	41%	−13.3	Frontal pole, inferior temporal gyrus, temporal pole, precentral gyrus, postcentral gyrus
55–64	84 221	42%	−15.1	Temporal pole, frontal pole, occipital pole
45–54	64 431	32%	−11.7	Temporal pole, postcentral gyrus, precentral gyrus, temporal fusiform cortex
Female participants (abdominal subcutaneous adipose tissue volume)				
75+	7792	4%	−5.61	Putamen, temporal pole, frontal pole, inferior temporal gyrus, parahippocampal gyrus
65–74	76 443	39%	−13.5	Temporal fusiform cortex, frontal pole, temporal pole, thalamus
55–74	71 481	36%	−19.2	Temporal pole, temporal fusiform cortex, frontal pole, occipital pole
45–54	8625	4%	−13.2	Temporal pole, angular gyrus, occipital pole, precentral gyrus, frontal pole
Male participants (visceral adipose tissue volume)				
75+	3206	2%	−5.17	Posterior cingulate gyrus, precentral gyrus, frontal pole
65–74	91 978	46%	−13.3	Temporal pole, frontal pole, postcentral gyrus, precentral gyrus, hippocampus
55–64	77 186	39%	−16.2	Temporal pole, thalamus, occipital pole, hippocampus
45–54	58 407	29%	−11.2	Temporal pole, occipital pole, postcentral gyrus, precentral gyrus
Female participants (visceral adipose tissue volume)				
75+	8341	4%	−5.43	Lateral occipital cortex, superior temporal gyrus, inferior frontal gyrus
65–74	116 513	59%	−15.2	Thalamus, temporal pole, frontal pole, frontal medial cortex
55–64	75 185	38%	−19.4	Temporal pole, frontal pole, frontal medial cortex, temporal fusiform cortex
45–54	5836	3%	−12.7	Occipital pole, temporal pole, angular gyrus, frontal pole

We demonstrate that cardiovascular risk has a detrimental influence on the brain between the ages of 55–74 years, and this association was weaker before 55 years and after 75 years in a bell-shaped curve (figure 6). In support of our finding, a deleterious effect of cardiovascular risk on cognition has been shown in those aged 50–64 years, but not in older adults.[25] Furthermore, obesity has been associated with an increased risk of dementia development in people under 65 years but not in later life.[26] Decreased BMI has been associated with an elevated dementia risk in later life.[27] While components of enhanced cardiovascular risk, such as increased BMI and low blood pressure, are detrimental to brain health in middle age, in later life these may be signatures of old age frailty. This may be attributable to two processes: (1) an initial direct effect on dementia development risk during midlife; and (2) then during later life, the lack of association may be a result of weight loss during the predementia phase.[28] We provide a novel evaluation including using MRI to evaluate volumetric brain changes and as a marker of obesity, and establish a sex difference with women affected by the deleterious effects of cardiovascular risk a decade later than males. While the precise mechanism by which the risk is reduced after 75 years is still unclear, it is very clear that targeting cardiovascular risk will have a significant benefit in preventing neurodegeneration. When evaluating APOE ε4 carriers and APOE ε4 non-carriers separately, the extensive relationship between cardiovascular risk/obesity and neurodegeneration remained.

Several markers of obesity including BMI and hip-to-waist ratio have been associated with an increased risk of dementia development,[29] although the results are mixed.[30] Here, visceral and subcutaneous fat was measured using abdominal MRI as a direct marker of obesity. An autopsy study, providing a direct measurement of abdominal fat, identified that greater abdominal fat was associated with a lower risk of cognitive impairment in those over 50.[31] Utilising MRI we were able to provide a direct measure of subcutaneous and visceral fat in vivo. In contrast, we demonstrated that greater subcutaneous and visceral fat was associated with reduced cortical volume. In males, these markers of obesity had an extensive influence on atrophy during the decades of 45–74 years. Visceral and subcutaneous adipose tissue volume showed strong associations with lower brain volumes in female participants aged 55–74 years. Thus, males may be more susceptible to the neurodegenerative influence of obesity in earlier decades of life. Visceral fat is associated with insulin resistance, inflammation, and oxidative stress,[32] suggesting multiple mechanisms may mediate the relationship between obesity and neuronal decline. This supports the proposition that obesity is an important modifiable risk factor to prevent neuronal damage and reduce the risk of dementia development.

The time course of cardiovascular risk mitigation could be imperative to the success of a therapeutic strategy. It is important to consider that separate cardiovascular risk factors may be detrimental via differing pathways; thus, there may be important differences in temporal dynamics that determine the success of potential cardiovascular risk mitigation strategies. Therefore, consideration of sex differences may be important for the time course of effective therapeutic strategies, with intervention targeting obesity perhaps required earlier in males. Future studies should aim to ascertain the influence of individual, modifiable cardiovascular risk factors on brain health and cognition during different decades of life.

Several mechanistic pathways may mediate the detrimental consequences of cardiovascular risk on brain health.

Cholesterol: In transgenic mouse models of Alzheimer's disease, diet-induced hypercholesterolaemia has been demonstrated to increase amyloid β (Aβ) accumulation.[33 34] Individuals with high cholesterol show a higher prevalence of senile plaques compared with people with low cholesterol.[35] Cholesterol could act as a catalyst that enhances the aggregation of Aβ, increasing its primary nucleation rate by up to 20-fold.[36] Changes in the cholesterol can cause changes in cell membrane properties. Lipid rafts are small dynamic assemblies highly enriched with cholesterol and sphingomyelin membrane microdomains with
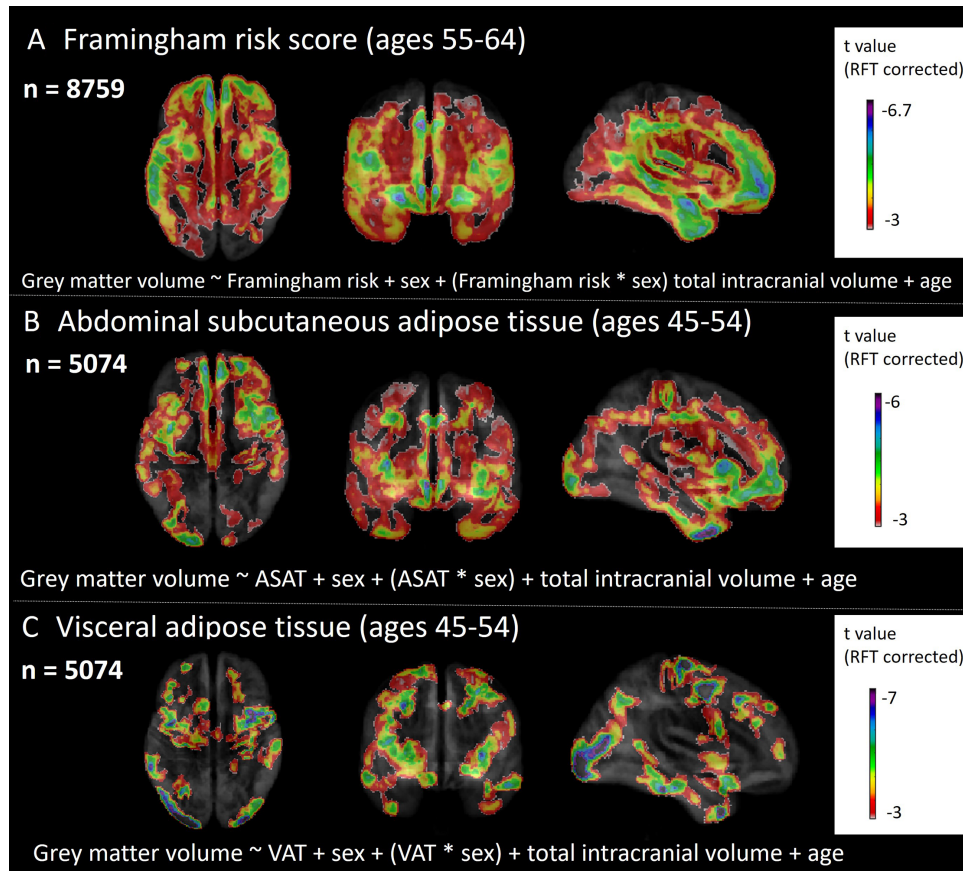
Figure 5 Cardiovascular risk and obesity associated with accelerated grey matter volume loss a decade earlier in males. (A) Interaction between Framingham risk score and sex on grey matter volume loss, indicating elevated neurodegeneration in males aged 55–64 years. (B) Interaction between abdominal subcutaneous adipose tissue and sex on grey matter volume, demonstrating elevated grey matter decline in males aged 45–54 years. (C) Interaction between visceral adipose tissue and sex on grey matter volume, demonstrating accelerated grey matter volume loss in males aged 45–54 years. ASAT, abdominal subcutaneous adipose tissue; RFT, random field theory; VAT, visceral adipose tissue.

an important role in Aβ formation.[37] Cholesterol within lipid rafts modulates amyloid precursor protein cleavage and, thus, influences the progression of Alzheimer's disease pathology.[38] The increased accumulation of cholesterol promotes the binding of amyloid precursor protein to the lipid rafts, leading to the production of Aβ following cleavage by BACE1 and γ-secretase.[39] It has also been shown that reducing the production of cholesterol reduces the production of cholesterol esters which reduces the amount of Aβ production.

Hypertension: Rodent models indicate that hypertension induces oxidative stress in the cerebrovasculature, which could lead to an upregulation of RAGE (receptor for advanced glycation end products) mRNA which has a critical role in controlling the transport of Aβ across the BBB.[40] Brain endothelial expression of RAGE is upregulated in both Alzheimer's disease mouse models and Alzheimer's disease patients.[41] Hypertension-induced RAGE activation in brain vessels has been shown to augment Aβ accumulation and result in cognitive impairment in

Table 4 Cluster information displaying the interaction between sex and Framingham risk score, abdominal subcutaneous adipose tissue volume, and visceral adipose tissue volume with lower brain volume

Decade (ages)	Total volume (voxels)	Percentage of total grey matter mask	Maximum T value	Peak regional associations
Framingham risk scores				
55–64	82 905	42%	−6.7	Frontal pole, planum temporale, temporal occipital fusiform cortex
65–75	9229	5%	−5.35	Juxtapositional lobule cortex, temporal fusiform cortex, frontal pole
Abdominal subcutaneous adipose tissue				
45–54	36 118	18%	−6.06	Temporal pole, frontal medial cortex, planum polare, occipital pole
55–64	18 471	9%	−7.19	Frontal pole, superior temporal gyrus, precentral gyrus, postcentral gyrus
65–74	15 090	8%	−6.6	Frontal pole, precentral gyrus, inferior temporal gyrus, anterior cingulate cortex
75+	5854	3%	6.18	Inferior temporal gyrus, occipital pole
Visceral adipose tissue				
45–54	16 748	8%	−6.97	Occipital pole, middle frontal gyrus, inferior temporal gyrus, postcentral gyrus
65–74	14 397	7%	6.81	Occipital pole, precuneus, parahippocampus
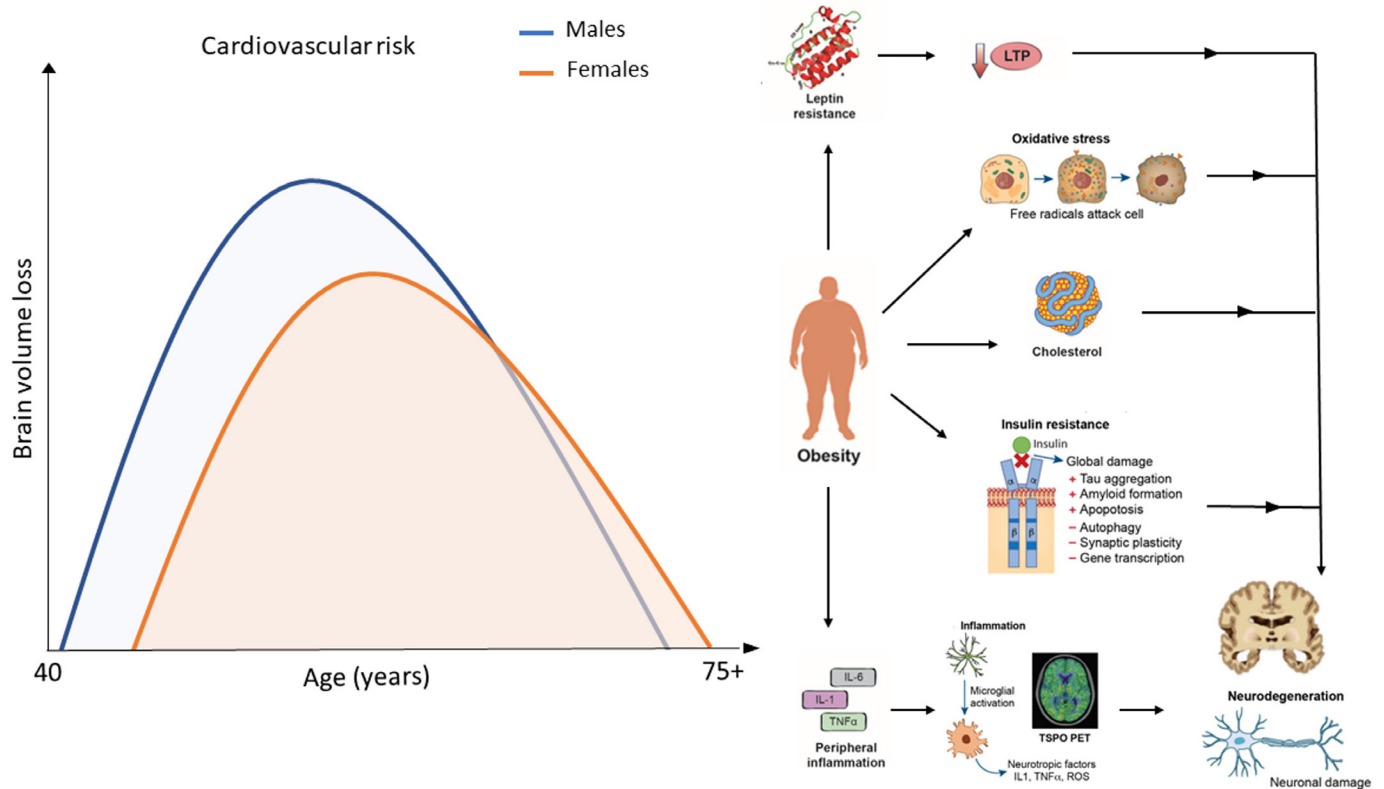
Figure 6 Graph of the timeframe and extent that cardiovascular risk factors influence neurodegenerative processes (brain volume loss) in males and females and depicts the mechanisms that cardiovascular risk induces brain atrophy. IL, interleukin; LTP, long-term potentiation; PET, positron emission tomography; ROS, reactive oxygen species; TNFα, tumour necrosis factor α; TSPO, translocator protein.

rodents.[40] Furthermore, in hypertensive mouse models, hypertension causes deterioration in the BBB and increases Aβ deposition in the hippocampus.[42] In postmortem evaluation, higher late-life systolic blood pressure was indicated to be associated with neurofibrillary tangles and Aβ plaques.[43]

Obesity: Aberrant inflammatory response in obesity may be related to Alzheimer's disease pathology via dysregulated endocrine homeostasis.[7] Subclinical inflammation arising from adipose tissue may interact with the cerebral inflammatory response, leading to neurodegeneration. Leptin signalling dysfunction in the brain may underlie the relationship between obesity and neurodegeneration. Leptin engages several intracellular pathways in the brain, including ERK, MAPK, PI3K and cAMP/PDE3B.[44] A variety of signalling pathways underlie the role of leptin in regulating synaptic activity, neuronal plasticity, survival and proliferation.[44] Therefore, loss of cerebral leptin signalling in obesity may contribute to neuronal loss, synaptic degeneration, and cognitive deficits.

Diabetes: Disrupted insulin signalling, a core feature of type 2 diabetes, may directly affect the brain.[45] Impaired insulin signalling reduces phosphorylation of protein kinase B, increasing GSK3β activity which can induce hyperphosphorylation of τ in the brain.[46] Deficient insulin transport across the BBB and/or diminished cerebral response to insulin can impair PI3K signalling, initiating the activation of inflammatory pathways.[47]

Implications

The strength of the relationship between cardiovascular risk and cerebral damage emphasises the potential for mitigating cardiovascular risk as a therapeutic strategy for Alzheimer's disease. One such possibility may be in the repurposing of agents used for obesity and type 2 diabetes mellitus for the treatment of Alzheimer's disease.[46 48] This includes glucagon-like-peptide-1 receptor agonists, highlighted as the most promising class of drugs for repositioning for Alzheimer's disease, with phase 3 evaluation of semaglutide in participants with early Alzheimer's disease underway (NCT04777396). Several alternative agents used for the treatment of cardiovascular disease appear to show promise for the treatment of Alzheimer's disease including antihypertensive medication, metformin, and intranasal insulin. However, some candidates such as angiotensin II receptor antagonists have failed to display efficacy in reducing brain volume loss.[49] A lack of therapeutic benefit may stem from the age group recruited in the trial. In the RADAR trial, 25% of participants were over 79 years old and a total of 63% of participants were 70 years or older.[49] Our data suggest that failed trials may have recruited participants unlikely to respond significantly to treatment. Targeting cardiovascular risk in the early stages of the disease may be essential to the success of future trials.

Study limitations

A limitation of the study is that the UK Biobank did not record Alzheimer's specific biomarkers, such as amyloid and τ burdens, so the influence on brain volume is non-disease specific. In this study, the maximum relationship between cardiovascular risk and loss of grey matter volume was largely shown in temporal and frontal areas, and only in those aged 75+ was the peak relationship located to the posterior cingulate cortex. As atrophy of frontal, parietal, and temporal regions is typical of normal ageing, it is difficult to differentiate the impact of cardiovascular risk on general accelerated ageing processes and the risk of specific neurodegenerative conditions. However, accelerated

atrophy to temporal lobe regions is strongly linked with the stage and intensity of Alzheimer's disease. Additionally, it should be noted that the lack of association in those aged 75+ could, in part, be due to the smaller sample size than other age bands evaluated in this study. Another limitation of the current study is that no direct comparison between APOE genotypes was performed.

CONCLUSIONS

Here, we demonstrate that enhanced cardiovascular risk, abdominal subcutaneous adipose tissue and visceral adipose tissue volumes show an extensive relationship with neurodegeneration across several decades of life following a bell-shaped time course. Several mechanisms, including inflammation, central leptin and insulin resistance as well as the breakdown of the BBB, may underlie this relationship and the subsequent neuronal damage. Mitigating cardiovascular risk represents a promising approach to treat or even prevent the development of Alzheimer's disease. Targeting cardiovascular risk and obesity a decade earlier in males than females may be imperative for potential candidates to achieve a therapeutic benefit in preventing neurodegeneration and cognitive decline.

Disclaimer Dissemination to participants and related patient and public communities. Results from UK Biobank are routinely disseminated to study participants via the study website and Twitter feed.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by UK Biobank and has ethical approval from the North West Multi-centre Research Ethics Committee (MREC) (approval number: 11/NW/0382). All participants gave informed consent. This analysis of data was performed under UK Biobank application ID87031. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. These data are available upon approved research from UK Biobank https://www.ukbiobank.ac.uk/. Data include a range of imaging, genetic, clinical, and demographic information on 500,000 participants. UK Biobank data are available to all bona fide researchers for all types of health-related research which is in the public interest. Researchers must register with UK Biobank by completing the registration form in the Access Management System (https://ams.ukbiobank.ac.uk/ams/).

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REFERENCES

1 Nichols E, Steinmetz JD, Vollset SE, *et al*. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health* 2022;7:e105–25.
2 DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. *Mol Neurodegener* 2019;14:32.
3 Buccellato FR, D'Anca M, Fenoglio C, *et al*. Role of Oxidative Damage in Alzheimer's Disease and Neurodegeneration: From Pathogenic Mechanisms to Biomarker Discovery. *Antioxidants (Basel)* 2021;10:1353.
4 Ju Y, Tam KY. Pathological mechanisms and therapeutic strategies for Alzheimer's disease. *Neural Regen Res* 2022;17:543–9.
5 Santos CY, Snyder PJ, Wu W-C, *et al*. Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: a review and synthesis. *Alzheimers Dement (Amst)* 2017;7:69–87.
6 Livingston G, Huntley J, Sommerlad A, *et al*. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 2020;396:413–46.
7 Pasqualetti G, Thayanandan T, Edison P. Influence of genetic and cardiometabolic risk factors in Alzheimer's disease. *Ageing Res Rev* 2022;81:101723.
8 McGuire MJ, Ishii M. Leptin Dysfunction and Alzheimer's Disease: Evidence from Cellular, Animal, and Human Studies. *Cell Mol Neurobiol* 2016;36:203–17.
9 Russo C, Valle MS, Russo A, *et al*. The Interplay between Ghrelin and Microglia in Neuroinflammation: Implications for Obesity and Neurodegenerative Diseases. *Int J Mol Sci* 2022;23:13432.
10 Zárate S, Stevnsner T, Gredilla R. Role of Estrogen and Other Sex Hormones in Brain Aging. Neuroprotection and DNA Repair. *Front Aging Neurosci* 2017;9:430.
11 van den Beld AW, Kaufman J-M, Zillikens MC, *et al*. The physiology of endocrine systems with ageing. *Lancet Diabetes Endocrinol* 2018;6:647–58.
12 Collins R. UK biobank: protocol for a large-scale prospective epidemiological resource. 2007.
13 D'Agostino RB Sr, Vasan RS, Pencina MJ, *et al*. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117:743–53.
14 Linge J, Borga M, West J, *et al*. Body Composition Profiling in the UK Biobank Imaging Study. *Obesity (Silver Spring)* 2018;26:1785–95.
15 Mittal B. Subcutaneous adipose tissue & visceral adipose tissue. *Indian J Med Res* 2019;149:571–3.
16 West J, Dahlqvist Leinhard O, Romu T, *et al*. Feasibility of MR-Based Body Composition Analysis in Large Scale Population Studies. *PLoS One* 2016;11:e0163332.
17 Miller KL, Alfaro-Almagro F, Bangerter NK, *et al*. Multimodal population brain imaging in the UK Biobank prospective epidemiological study. *Nat Neurosci* 2016;19:1523–36.
18 Gentili C, Cecchetti L, Handjaras G, *et al*. The case for preregistering all region of interest (ROI) analyses in neuroimaging research. *Eur J Neurosci* 2021;53:357–61.
19 Peelle JE, Cusack R, Henson RNA. Adjusting for global effects in voxel-based morphometry: gray matter decline in normal aging. *Neuroimage* 2012;60:1503–16.
20 Crowley S, Huang H, Tanner J, *et al*. Considering total intracranial volume and other nuisance variables in brain voxel based morphometry in idiopathic PD. *Brain Imaging Behav* 2018;12:1–12.
21 Dale AM, Fischl B, Sereno MI. Cortical Surface-Based Analysis. *Neuroimage* 1999;9:179–94.
22 Buckner RL, Head D, Parker J, *et al*. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. *Neuroimage* 2004;23:724–38.
23 Mathotaarachchi S, Wang S, Shin M, *et al*. VoxelStats: A MATLAB Package for Multi-Modal Voxel-Wise Brain Image Analysis. *Front Neuroinform* 2016;10:20.
24 Song R, Pan K-Y, Xu H, *et al*. Association of cardiovascular risk burden with risk of dementia and brain pathologies: a population-based cohort study. *Alzheimers Dement* 2021;17:1914–22.
25 Olaya B, Moneta MV, Bobak M, *et al*. Cardiovascular risk factors and memory decline in middle-aged and older adults: the English Longitudinal Study of Ageing. *BMC Geriatr* 2019;19:337.
26 Pedditzi E, Peters R, Beckett N. The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies. *Age Ageing* 2016;45:14–21.
27 Li J, Liu C, Ang TFA, *et al*. BMI decline patterns and relation to dementia risk across four decades of follow-up in the Framingham Study. *Alzheimers Dement* 2023;19:2520–7.
28 Kivimäki M, Luukkonen R, Batty GD, *et al*. Body mass index and risk of dementia: analysis of individual-level data from 1.3 million individuals. *Alzheimers Dement* 2018;14:601–9.
29 Tang X, Zhao W, Lu M, *et al*. Relationship between Central Obesity and the incidence of Cognitive Impairment and Dementia from Cohort Studies Involving 5,060,687 Participants. *Neurosci Biobehav Rev* 2021;130:301–13.
30 Gustafson DR, Luchsinger JA. High adiposity: risk factor for dementia and Alzheimer's disease? *Alzheimers Res Ther* 2013;5:57.

31 Nishizawa A, Cuelho A, de Farias-Itao DS, *et al*. Direct Measurements of Abdominal Visceral Fat and Cognitive Impairment in Late Life: Findings From an Autopsy Study. *Front Aging Neurosci* 2019;11:109.

32 Abraham TM, Pedley A, Massaro JM, *et al*. Association between visceral and subcutaneous adipose depots and incident cardiovascular disease risk factors. *Circulation* 2015;132:1639–47.

33 Levin-Allerhand JA, Lominska CE, Smith JD. Increased amyloid- levels in APPSWE transgenic mice treated chronically with a physiological high-fat high-cholesterol diet. *J Nutr Health Aging* 2002;6:315–9.

34 Refolo LM, Malester B, LaFrancois J, *et al*. Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model. *Neurobiol Dis* 2000;7:321–31.

35 Matsuzaki T, Sasaki K, Hata J, *et al*. Association of Alzheimer disease pathology with abnormal lipid metabolism: the Hisayama Study. *Neurology* 2011;77:1068–75.

36 Habchi J, Chia S, Galvagnion C, *et al*. Cholesterol catalyses Aβ42 aggregation through a heterogeneous nucleation pathway in the presence of lipid membranes. *Nat Chem* 2018;10:673–83.

37 Rudajev V, Novotny J. Cholesterol as a key player in amyloid β-mediated toxicity in Alzheimer's disease. *Front Mol Neurosci* 2022;15:937056.

38 Hicks DA, Nalivaeva NN, Turner AJ. Lipid rafts and Alzheimer's disease: protein-lipid interactions and perturbation of signaling. *Front Physiol* 2012;3:189.

39 Beel AJ, Sakakura M, Barrett PJ, *et al*. Direct binding of cholesterol to the amyloid precursor protein: an important interaction in lipid-Alzheimer's disease relationships? *Biochim Biophys Acta* 2010;1801:975–82.

40 Carnevale D, Mascio G, D'Andrea I, *et al*. Hypertension induces brain β-amyloid accumulation, cognitive impairment, and memory deterioration through activation of receptor for advanced glycation end products in brain vasculature. *Hypertension* 2012;60:188–97.

41 Deane R, Bell RD, Sagare A, *et al*. Clearance of amyloid-beta peptide across the blood-brain barrier: implication for therapies in Alzheimer's disease. *CNS Neurol Disord Drug Targets* 2009;8:16–30.

42 Gentile MT, Poulet R, Di Pardo A, *et al*. Beta-amyloid deposition in brain is enhanced in mouse models of arterial hypertension. *Neurobiol Aging* 2009;30:222–8.

43 Arvanitakis Z, Capuano AW, Lamar M, *et al*. Late-life blood pressure association with cerebrovascular and Alzheimer disease pathology. *Neurology* 2018;91:e517–25.

44 Morrison CD. Leptin signaling in brain: a link between nutrition and cognition?. *Biochim Biophys Acta* 2009;1792:401–8.

45 Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. *Nat Rev Endocrinol* 2018;14:591–604.

46 Nowell J, Blunt E, Gupta D, *et al*. Antidiabetic agents as a novel treatment for Alzheimer's and Parkinson's disease. *Ageing Res Rev* 2023;89:101979.

47 Huang X, Liu G, Guo J, *et al*. The PI3K/AKT pathway in obesity and type 2 diabetes. *Int J Biol Sci* 2018;14:1483–96.

48 Nowell J, Blunt E, Edison P. Incretin and insulin signaling as novel therapeutic targets for Alzheimer's and Parkinson's disease. *Mol Psychiatry* 2023;28:217–29.

49 Kehoe PG, Turner N, Howden B, *et al*. Safety and efficacy of losartan for the reduction of brain atrophy in clinically diagnosed Alzheimer's disease (the RADAR trial): a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Neurol* 2021;20:895–906.